

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 August 2001 (02.08.2001)

PCT

(10) International Publication Number
WO 01/55109 A1

(51) International Patent Classification⁷: C07D 209/18,
A61K 31/405, A61P 3/04, C07D 209/40, 317/60, A61K
31/36, C07C 233/40, C07D 401/12, 213/61, A61K 31/44,
C07D 207/34, A61K 31/34, C07D 231/56, A61K 31/415,
C07D 403/12

Ivars [LV/LV]; Miera Street 17-8, LV-2169 Salaspils
(LV).

(21) International Application Number: PCT/GB01/00350

(22) International Filing Date: 29 January 2001 (29.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0002059.4 28 January 2000 (28.01.2000) GB

(74) Agents: PETT, Christopher, Phineas et al.; Frank B.
Dehn & Co., 179 Queen Victoria Street, London EC4 4EL
(GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*):
MELACURE THERAPEUTICS AB [SE/SE]; Ulleråks-
crsvägen 38, S-756 43 Uppsala (SE).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): LUNDSTEDT,
Torbjörn [SE/SE]; Granelidsvägen 7B, S-756 55 Uppsala
(SE). SKOTTNER, Anna [SE/SE]; Lobov. 3, S-178 32
Ekerö (SE). SEIFERT, Elisabeth [SE/SE]; Rotyxv. 17,
S-756 48 Uppsala (SE). STARCHENKOV, Igor [—/LV];
Kveles iela 15/10-3, LV-1024 Riga (LV). KALVINS,

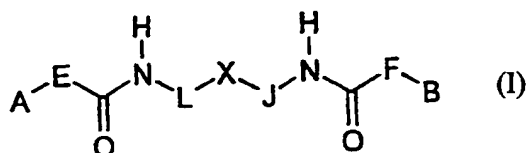
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/55109 A1

(54) Title: AROMATIC AMIDES ACTING ON MELANOCORTIN RECEPTORS



(57) Abstract: The present invention relates to novel aromatic amides of formula (I) and to the use of these amides for the treatment of obesity, anorexia, inflammation, mental disorders and other diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

AROMATIC AMIDES ACTING ON MELANOCORTIN RECEPTORS

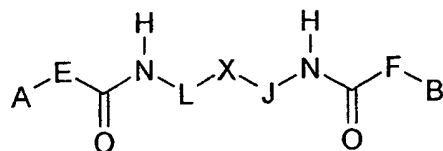
The present invention relates to novel aromatic amines and to the use of these amines
5 for the treatment of obesity, anorexia, inflammation, mental disorders and other
diseases associated with the melanocortin receptors or related systems, e.g. the
melanocyte stimulating hormones.

A number of large linear and cyclic peptides are known in the art which show high
10 specific binding to melanocortin (MC) receptors. The agonistic and/or antagonistic
properties of these peptides are also known. See for example "Melanocortin Receptor
ligands and methods of using same" by Dooley, Girtten and Houghten (WO99/21571).
Two patent applications (WO 99/55679 and WO 99/64002) have been published which
include small molecules showing activity on the melanocortin receptors. However, the
15 compounds in the present invention are structuarly different from the previously
published melanocortin agonists, and hence the observed effects are unexpected.

One aspect of the present invention is therefore to provide low molecular weight
compounds showing activity on melanocortin receptors and which may be taken up
20 after per oral administration and which may penetrate well through the blood brain
barrier.

The present invention provides novel compounds of the general formula (I):

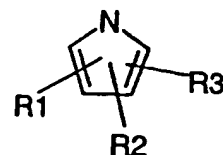
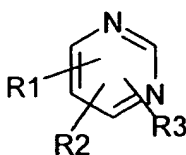
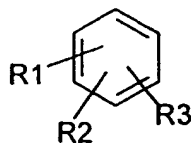
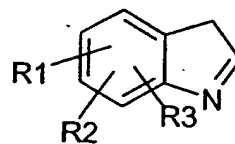
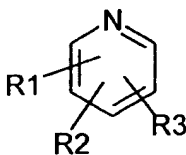
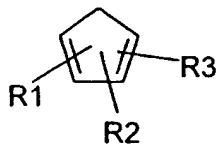
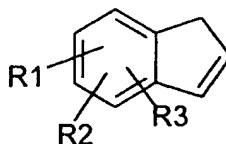
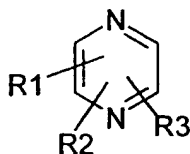
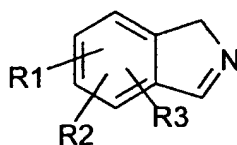
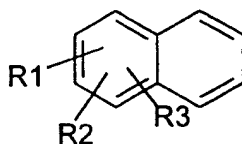
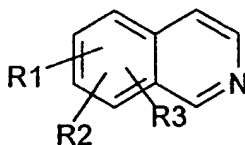
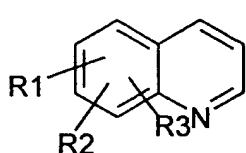
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wherein E, L, J and F are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4 or 5 carbon atoms.

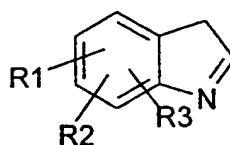
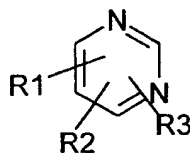
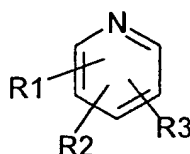
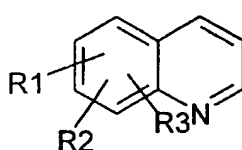
- Examples of E, L, J and F include straight or branched chain alkyl and alkene groups, optionally substituted by one or more halogen atoms, preferably chlorine.
- Preferred examples of E, L, J and F include methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl and iso-pentyl, and the corresponding alkene groups.

- 10 A and B are the same or different and are independently selected from the following:



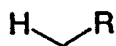
wherein R_1 , R_2 and R_3 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 5 carbon atoms, electron donor groups such as alkoxy having 1-5 carbon atoms or hydroxy, electron acceptor groups selected from cyano, nitro, trifluoroalkyl or amide

Preferably, A and B are the same or different and are selected from the following:



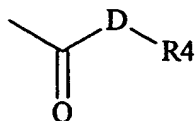
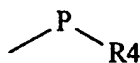
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X is selected from methylene, amino, carbonyl, nitrogen, oxygen, or from the following:



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R is selected from the following:



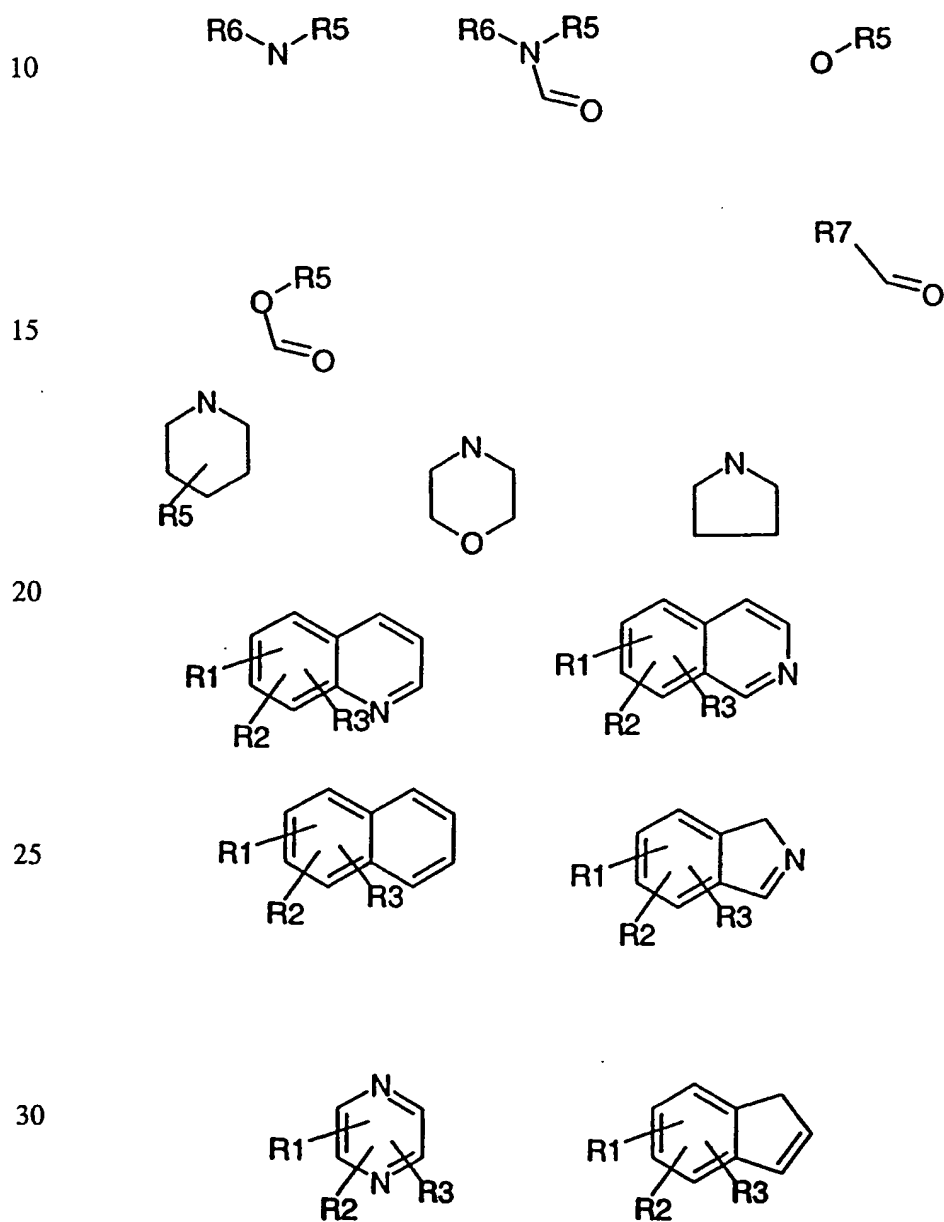
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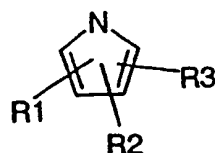
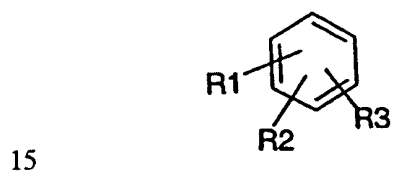
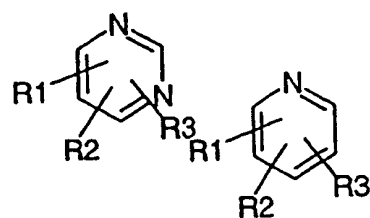
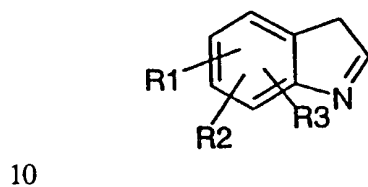
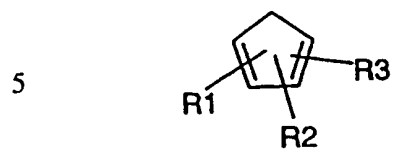
wherein P and D are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4 or 5 carbon atoms, or D may be absent (i.e. D is a single bond).

Examples of P and D include straight or branched chain alkyl and alkene groups, optionally substituted by one or more halogen atoms, preferably chlorine.

Preferred examples of P and D include methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl and iso-pentyl, and the corresponding alkene groups.

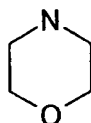
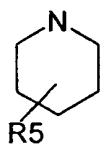
R4 is hydroxy, methyl, cyclohexyl, cyclopentyl, aminoguanidine, carboxylic or R4 is selected from:





20 R5 and R6 are the same or different and are selected from hydrogen, lower alkyl such as methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl, iso-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and hexyl; and R1, R2 and R3 are as defined above.

25 R7 is selected from:



In cases where A and/or B are bicyclic groups, it should be noted that R1, R2 and R3 represent substituents which may be present on either of the rings.

Furthermore, it should be noted that A and B may be attached in the carbon backbone of the compound of general formula (I) at any suitable point within A or B, preferably at the 1, 2 or 3 position; and most preferably A and/or B are not attached in the carbon backbone via an N-atom in A and/or B.

The invention also encompasses pharmacologically active salts of the compounds of general formula (I).

10

When used in the foregoing definitions, the term alkyl is meant to include straight or branched chain hydrocarbon groups; the term alkoxy is meant to include straight or branched chain alkoxy groups; and the term halogen includes fluoro, chloro or bromo.

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Preferably, the "alkyl having 1 to 5 carbon atoms" is a lower alkyl such as methyl, ethyl, propyl or iso-propyl.

Preferably, the "alkoxy having 1 to 5 carbon atoms" is a lower alkoxy such as methoxy, ethoxy, propoxy or iso-propoxy.

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Preferably, the halogen is fluoro or chloro.

Preferably, the trifluoroalkyl is trifluoromethyl, trifluoroethyl, trifluoropropyl or trifluoroiso-propyl.

25

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active acid addition salts by treatment with appropriate acids, e.g. inorganic acids such as hydrochloric, hydrobromic, sulphuric, nitric and phosphoric acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, succinic, fumaric, tartaric, citric and palmoic acid.

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Conversely, the salt form may be converted into the free base form by treatment with alkali.

5 The present invention relates novel aromatic amines. Some of the compounds of the present invention have been biologically tested in the melanocortin system and have surprisingly been shown to be capable of binding to melanocortin receptors as well as showing activity in functional assays.

10 Some of the compounds of the present invention are either agonists or antagonists of a specific MC-receptor or of a number of MC-receptors, e.g. MC1, MC3, MC4 or/and MC5 receptors.

15 The MC-receptors belong to the class of G-protein coupled receptors which are all built from a single polypeptide forming 7 transmembrane domains. Five such receptors types, termed MC1, MC2, MC3, MC4 and MC5, have been described. The MC receptor's signaling is mainly mediated via cAMP but also other signal transduction pathways are known. They are distinctly distributed in the body.

20 MC-receptors are linked to a variety of physiological actions that are thought to be mediated by distinct subtypes of the MC-receptors. In many cases, however, it is not entirely clear which of the subtypes is responsible for the effect.

25 It has long been known that MSH-peptides may affect many different processes such as motivation, learning, memory, behaviour, inflammation, body temperature, pain perception, blood pressure, heart rate, vascular tone, brain blood flow, nerve growth, placental development, aldosterone synthesis and release, thyroxin release, spermatogenesis, ovarian weight, prolactin and FSH secretion, uterine bleeding in women, sebum and pheromone secretion, blood glucose levels, intrauterine foetal growth, as well as other events surrounding parturition (Eberle, AN: The
30 melanotropins: Chemistry, physiology and mechanisms of action. Basel: Karger, Switzerland. 1988, ISBN 3-8055-4678-5; Gruber, and Callahan, Am. J. Physiol. 1989,

257, R681-R694; De Wildt et al., J. Cardiovascular Pharmacology. 1995, 25, 898-905), as well as inducing natriuresis (Lin et al., Hypertension. 1987, 10, 619-627).

It is also well-known that the immunomodulatory action of α -MSH includes both immuno-stimulatory and immunosuppressive effects. Several studies have shown that α -MSH antagonizes the effects of pro-inflammatory cytokines such as IL-1 α , IL-1 β , IL-6 and TNF α , and induces the production of the anti-inflammatory cytokine, IL-10 (for review see Catania & Lipton, 1993).

Eating behaviour is regulated by a complex network of physiological regulatory pathways that involve both the central nervous system and peripheral sites. Factors such as leptin, insulin, NPY (neuropeptide Y), orexins, CRF (Corticotropin-Releasing Factor, release hormone) and melanocortic peptides (Schwartz: Nature Medicine 1998, 4, 385-386) are known to control the amount of food intake both during short and long term, which may affect body weight, body fat mass and growth rate. Recent studies have shown a role of MC-receptors, especially the MC4 receptor, for control of food intake, and there is evidence indicating that the melanocortins and the MC4 receptor are important factors downstream of leptin. Intracerebroventricular injections of the melanocortic peptides α -MSH and ACTH(1-24) have been shown to markedly inhibit feeding (Poggioli et al., Peptides, 1986, 7, 843-848; Vergoni et al., Neuropeptides, 1986, 7, 153-158).

The MC5-receptor has recently been attributed a role in control of exocrine gland function (van der Kraan, et al., Endocrinol. 1998, 139, 2348-2355; Chen et al., Cell. 1997, 91, 789-798).

In addition, the melanocortic peptides have distinct effects on sexual functions in that they cause erection in males (Donovan, Psychol. Med. 1978, 8, 305-316), presumably mediated by a central agonistic effect of the peptide on MC-receptors. It has also been shown that a MC-receptor blocker could inhibit the erectogenic effect of melanocortic peptides (Vergoni et al., Eur. J. Pharmacol, 1998, 362; 95-101).

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of mental disorders such as psychoses, depression, anxiety, senile
5 dementia, Alzheimer's disease, drug abuse disorders and eating disorders such as anorexia and bulimia.

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the
10 treatment of dysfunctions of the endocrine system and other hormonal systems such as excessive menstruations, endometriosis, events related to parturition, dysfunctions related to prolactin, dysfunctions related to growth hormone, dysfunctions related to testosterone, dysfunctions related to estrogen, dysfunctions related to glucocorticoids, dysfunctions related to luteinizing hormone and follicle
15 stimulating hormone, inducing abortion, for prevention of abortion and/or for treatment of events related to parturition.

Others of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the
20 treatment of sexual functions / dysfunctions such as inducing erection in man, to induce erection in animal breeding, to stimulate intercourse in animals which are difficult to mate, in particular rare species or valuable strains, pets, cats, dogs, horses or to reduce sexual behaviour in animals, e.g. for pets, cats etc., to treat impotence and disorders related to sexual drive, including lack of sexual drive or
25 abnormal sexual drive in both men and women.

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of inflammation such as inflammations related to the production of nitric
30 oxide, inflammation related to increased amounts (upregulated amounts) of inducible nitric oxide synthase, inflammation related to activation of transcriptional activators, inflammation related to nuclear factor kappa beta. inflammation related

to macrophages, neutrophils, monocytes, keratinocytes, fibroblasts, melanocytes, pigment cells and endothelial cells, inflammation related to increased production and/or release of inflammatory cytokines, such as e.g. interleukins, in particular interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α).

5

In the present specification, "increased production" refers to increased formation, increased release, or increased amount of an endogenous compound locally, regionally or systemically in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "upregulated" refers to an increased

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activity or amount of the compound compared with that in a healthy individual.

In the present specification, "decreased production" refers to decreased formation, decreased release, or decreased amount of an endogenous compound in a patient compared to the amount of said endogenous compound in a healthy individual. In the

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present specification, "downregulated" refers to a decreased activity or amount of the compound compared with that in a healthy individual.

In particular, positive treatment effects or preventive effects may be seen in conditions where inflammation or an inflammatory-like condition is caused by or being associated

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with one or more of the following: allergy, hypersensitivity, bacterial infection, viral infection, inflammation caused by toxic agent, fever, autoimmune disease, radiation damage by any source including UV-radiation, X-ray radiation, γ -radiation, α - or β -particles, sun burns, elevated temperature or mechanical injury. Moreover, inflammation due to hypoxia, which is optionally followed by reoxygenation of the

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hypoxic area, is typically followed by severe inflammation, which condition may be positively affected by treatment with a compound of the invention.

In very specific embodiments of the invention, a compound of the invention may be administered for the prevention or therapeutic treatment of inflammatory diseases of

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the skin (including the dermis and epidermis) of any origin, including skin diseases having an inflammatory component. Specific examples of this embodiment of the invention include treatment of contact dermatitis of the skin, sunburns of the skin.

burns of any cause, and inflammation of the skin caused by chemical agents, psoriasis, vasculitis, pyoderma gangrenosum, discoid lupus erythematosus, eczema, pustulosis palmo-plantaris, and pemphigus vulgaris.

- 5 Also comprised by the invention is the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of an inflammatory disease in the abdomen, including an abdominal disease having an inflammatory component. Specific examples of the treatment of such a disease with a compound of the invention are gastritis, including one of unknown origin, gastritis perniciousa
10 (atrophic gastritis), ulcerous colitis (colitis ulcerosa), morbus Crohn, systemic sclerosis, ulcus duodeni, coeliac disease, oesophagitis and ulcus ventriculi.

- Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of systemic or general
15 and/or local immunological diseases, including those of an autoimmune nature, and other inflammatory diseases of a general nature. Specific examples include treatment of rheumatoid arthritis, psoriatic arthritis, systemic sclerosis, polymyalgia rheumatica, Wegener's granulomatosis, sarcoidosis, eosinophilic fasciitis, reactive arthritis, Bechterew's disease, systemic lupus erythematosus, arteritis temporalis. Behcet's
20 disease, morbus Burger, Good Pastures' syndrome, eosinophilic granuloma, fibromyalgia, myositis, and mixed connective tissue disease. Included therein is also arthritis, including arthritis of unknown origin.

- Further included in the invention is administration of a compound of formula (I) or a
25 pharmacologically acceptable salt thereof for the treatment of a disease of the peripheral and/or central nervous system related to inflammation. Included in this aspect of the invention is the treatment of cerebral vasculitis, multiple sclerosis, autoimmune ophthalmitis and polyneuropathia. Comprised by the invention is also the administration of a compound of the invention for the treatment of an inflammation of
30 the central nervous system to prevent apoptotic cell death. Moreover, as some of the compounds of the invention show a distinct ability to induce nerve regeneration, positive treatment effects are often seen in central nervous system diseases involving

damage of cells in this region. This aspect of the invention also includes treatment of traumatic injuries to the central nervous system, brain edema, multiple sclerosis, Alzheimer's disease, bacterial and viral infections in the central nervous system, stroke, and haemorrhagia in the central nervous system.

5

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the eye and tear glands related to inflammation. Specific examples of such diseases comprise anterior and posterior uveitis, retinal vasculitis, optic neuritis, optic neuromyelitis, Wegener's granulomatosis, Sjögren's syndrome, episcleritis, scleritis, sarcoidosis affecting the eye and polychondritis affecting the eye.

10

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the ear related to inflammation, specific examples of which include polychondritis affecting the ear and external otitis.

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Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the nose related to inflammation, specific examples of which are sarcoidosis, polychondritis and mid-line granuloma of the nose.

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Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the mouth, pharynx and salivary glands. Specific examples include Wegener's granulomatosis, mid-line granuloma, Sjögren's syndrome and polychondritis in these areas.

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Included in the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation in the lung. Specific examples include treatment of idiopathic alveolitis, primary pulmonary hypertension, bronchitis, chronic bronchitis, sarcoidosis, alveolitis

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in inflammatory systemic disease, pulmonary hypertension in inflammatory systemic disease, Wegener's granulomatosis and Good Pastures' syndrome.

Comprised by the invention is also the administration of a compound of formula (I) or
5 a pharmacologically acceptable salt thereof for the treatment of diseases related to the
inflammation of the heart. Specific examples include treatment of pericarditis,
idiopathic pericarditis, myocarditis, Takayasu's arteritis, Kawasaki's disease, coronary
artery vasculitis, pericarditis in inflammatory systemic disease, myocarditis in
inflammatory systemic disease, endocarditis and endocarditis in inflammatory systemic
10 disease.

Comprised by the invention is also the administration of a compound of formula (I) or
a pharmacologically acceptable salt thereof for the treatment of diseases related to
inflammation of the liver. Specific examples include treatment of hepatitis, chronic
15 active hepatitis, biliary cirrhosis, hepatic damage by toxic agents, interferon induced
hepatitis, hepatitis induced by viral infection, liver damage induced by anoxia and liver
damage caused by mechanical trauma.

Comprised by the invention is also the administration of a compound of formula (I) or
20 a pharmacologically acceptable salt thereof for the treatment of diseases related to
inflammation of the pancreas. Specific examples include treatment (and prevention) of
diabetes mellitus, acute pancreatitis and chronic pancreatitis.

Comprised by the invention is also the administration of a compound of formula (I) or
25 a pharmacologically acceptable salt thereof for the treatment of diseases related to the
inflammation of the thyroid. Specific examples of these embodiments of the
invention include treatment of thyroiditis, autoimmune thyroiditis and Hashimoto's
thyroiditis.

30 Comprised by the invention is also the administration of a compound of formula (I) or
a pharmacologically acceptable salt thereof for the treatment of diseases related to
inflammation of the kidney. Specific examples include treatment of

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glomerulonephritis, glomerulonephritis in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, Good-Pastures' syndrome, HLAB27 associated diseases, IgA nephritis (IgA = Immunoglobulin A), pyelonephritis, chronic pyelonephritis and interstitial nephritis.

5

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the joints. Specific examples include treatment of Bechterew's disease, psoriatic arthritis, rheumatoid arthritis, arthritis in colitis ulcerosa, arthritis in morbus Crohn, affection of joints in systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, reactive arthritis, Reiter's syndrome. Moreover, included in this embodiment of the invention is treatment of arthrosis of any joint, in particular arthrosis of finger joints, the knee and the hip.

10

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of blood vessels. Specific examples include treatment of arteritis temporalis, periarteritis nodosa, arteriosclerosis, Takayasu's arteritis and Kawasaki's disease. Particularly advantageous is the capacity of some compounds of the invention to afford protection against and prevention of arteriosclerosis. This is in part due to the capacity of some compounds of formula (I) or the pharmacologically acceptable salts thereof to prevent the induction of inducible nitric oxide synthesis (iNOS) caused by the action of oxidized Low Density Lipoprotein on endothelial cells and blood vessel walls.

20

25

Comprised by the invention is also the administration of a compound of the invention for the treatment of drug-induced disorders of the blood and lymphoid system, including the treatment of drug-induced hypersensitivity (including drug hypersensitivity) affecting blood cells and blood cell forming organs (e.g. bone marrow and lymphoid tissue). Specific embodiments of this aspect of the invention include the treatment of anemia, granulocytopenia, thrombocytopenia, leukopenia, aplastic anemia,

30

autoimmune hemolytic anemia, autoimmune thrombocytopenia and autoimmune granulocytopenia.

5 The compounds of the invention may also be administered for the treatment of fast allergic disorders (Type I allergy). Included in this embodiment of the invention is the treatment of anaphylactic reactions, anaphylactoid reactions, asthma, asthma of allergic type, asthma of unknown origin, rhinitis, hay fever and pollen allergy.

10 Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of inflammation related to infections of any origin. Specific examples include treatment of inflammation secondary to infection caused by virus, bacteria, helminths and protozoae.

15 Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of inflammations related to trauma and/or tissue injury of any origin.

20 Some of the compounds of formula (I) or pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of disorders of the cardiovascular system such as disorders related to blood pressure, heart rate, vascular tone, natriuresis, bleeding, shock, disorders related to ischemia, infarction, reperfusion injuries, arrhythmias of the heart, in particular during ischemia, or for the treatment of arrhythmias associated with reoxygenation of a previously ischemic period of the heart.

25

Some of the compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of pain such as pain of central origin, pain seen after damage to the CNS, stroke, infarction, pain of peripheral origin, chronic pain, neuropathies and
30 disorders where a treatment effect is achieved by stimulation of receptors in the periaqueductal grey area.

Because of the capacity of some of the compounds of the invention to stimulate pigment formation in epidermal cells, some of the compounds of the invention may be also useful for inducing skin tanning for cosmetic reasons, for treatment of vitiligo, or any other condition where darkening of skin color is desired. Moreover, because of the ability of some of the compounds of the invention to inhibit pigment formation in cells of the skin, they may also be useful for inducing lighter skin color for cosmetic reasons, or during any condition where a lighter color of skin is desired.

Some of the compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful to cause skin tanning, darkening the colour of the skin, to induce melanin synthesis in the skin, to reduce skin tanning, lightening the colour of the skin, to reduce or block melanin synthesis in the skin, to cause anti-inflammatory actions in the skin, to modulate epidermal growth, to improve wound healing, to treat acne, seborrhoea, acne roseacea, conditions related to malfunctions of the glands of the skin, e.g. sebaceous glands and over or underproduction of sebum.

Some of the compounds of the invention are useful for inhibiting or stimulating the *in vivo* formation of second messenger elements such as cAMP. Such inhibition/stimulation may be used in cells or crushed cell systems *in vitro*, e.g. for analytical or diagnostic purposes.

For analytical and diagnostic purposes the compounds of the invention may be used in radioactive form where they comprise one or more radioactive labels or gamma or positron emitting isotopes, to be used in radioligand binding for the quantification as well as tissue localisation of MC-receptors, for analysis of dissociation/association constants, and for imaging of *in vivo* binding by the use of scintigraphy, positron emission tomography (PET) or single photon emission computed tomography (SPECT), or for the diagnosis of disease and treatment of any malignancy where the malignant cells contain MC receptors.

Alternatively the compounds of the invention can be labelled with any other type of label that allows detection of the respective compound, e.g. fluorescence, biotin, or labels activated by gamma-irradiation, light photons or biochemical processes, or by light or UV-light (the latter in order to obtain a compound useful for covalent
5 labelling of MC receptors by a photoaffinity technique).

Some of the compounds of formula (I) or the pharmacologically acceptable salts thereof may also be tagged with a toxic agent (i.e. doxorubicin, ricin, diphtheria toxin or other) and used for targeted delivery to malignant cells bearing MC
10 receptors, or tagged with a compound capable of activating the endogenous immune system for triggering the immune system (for example a compound, monoclonal antibody or other, capable of binding to a T-cell antigen, e.g. CD3 or other) for treatment of malignancies and other MC receptor expressing diseases. The thus formed hybrid compound will direct cytotoxic cells to the malignant
15 melanoma cells or the MC1-receptor bearing malignant cells and inhibit the tumor growth.

Some of the compounds of formula (I) or a pharmacologically acceptable salt thereof may be attached to the antibody chemically by covalent or non-covalent bond(s).
20

Some of the compounds of the invention may be used for the treatment and diagnosis of diseases, disorders and/or pathological conditions in an animal, in particular in man.

The present invention also relates to a pro-drug which, upon administration to an
25 animal or a human, is converted to a compound of the invention. Pro-drugs of the compounds of formula (I) and their pharmacologically acceptable salts may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below.

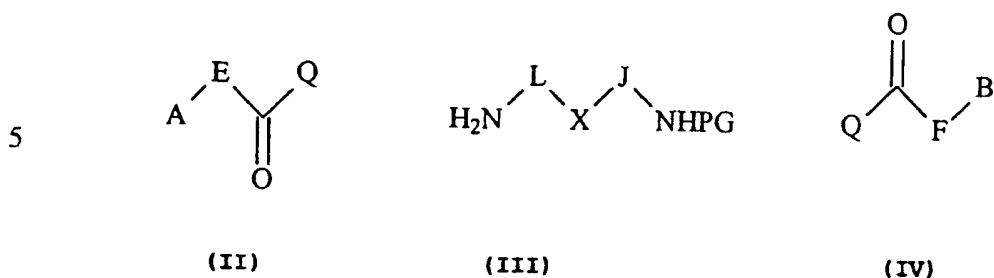
30 The compounds of the present invention may be bound covalently or non-covalently to one or several of other molecule(s) of any desired structure(s); the thus formed modified compound or complex may be used for the same purposes as described in

this specification for the compounds of the invention, as well as is disclosed in the Examples given below. In a particularly important embodiment of the invention, a radioactively-labeled molecule is covalently bound to a compound of formula (I) or a pharmacologically acceptable salt thereof so as to make a compound of formula (I) or a pharmacologically acceptable salt thereof radioactively labeled.

Some of the compounds of the invention bind to one or more MC-receptors. By the term "bind to one or more MC-receptors" is in this context intended a capacity of the compound of the invention to compete for the binding of [¹²⁵I]NDP-MSH at an MC-receptor, the MC-receptor preferably being one selected from the MC1, MC3, MC4 and/or MC5-receptors, using a binding assay such as that described in Example 2. In a further meaning, the term "bind to one or more MC-receptors" is in this context intended that the K_i-value of the compound of the invention, determined using a method such as that described in Example 2, is less than 1,000,000 nM, preferably less than 100,000 nM, more preferably less than 10,000 nM, somewhat more preferably less than 1,000 nM, even somewhat preferably less than 100 nM, and most preferably less than 50 nM. Most preferably, the compound of the invention has a K_i of less than 1,000 nM or less than 50 nM for a melanocortin receptor.

The invention also relates to methods for the manufacture and pharmaceutical preparations comprising one or more of the compounds of the invention, as well as to their uses for various medical and veterinary practices related to melanocyte stimulating hormone receptors.

The compounds of general formula (I) may be prepared by the following methods:

Method 1.

10 A compound with formula (II), wherein A and E are as previously defined and Q is a leaving group, is reacted with a compound of formula (III), wherein L, J and X are as previously defined and PG is a protecting group. Then the protecting group is removed by standard procedures and followed by a reacting with compound (IV), wherein F and B are as previously defined and Q is a suitable leaving group.

15

Legends to the Figures

Figures 1-4 Effects of MTII and Compound 1:2 on food intake and body weight gain.

20

Figure 5 Long term effects on food intake after a single icv administration of Compound 1:2.

Figures 6-7 Effects of Compound 1:15 on food intake and body weight gain.

25

Figure 8 Blocking the effect of Compound 1:2 with an MC4 receptor antagonist in vivo.

30 Examples

The following examples are intended to illustrate but not to limit the scope of the invention, although the compounds named are of particular interest for the

intended purposes. These compounds have been designated by a number code, a:b, where a means the number of the Example where the preparation of the compound is described, and b refers to the order of the compound prepared according to that example. Thus Example 1:2 means the second compound prepared according to

5 Example 1.

The structures of the compounds were confirmed by IR, NMR, MS and elementary analysis. When melting points are given, these are uncorrected.

10 **Example 1:1**

3-(1H-Indol-3-yl)-N-{2-[2-(3-1H-indol-3-yl-propionylamino)-ethylamino]-ethyl}-propionamide acetate

15 To a cooled to -22°C solution of diethylenetriamine (0.10g, 1mmol) in CH₂Cl₂ (8ml) was added 3-(1H-indol-3-yl)-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester (0.57g, 2mmol).

The reaction mixture was stirred for 1h at the same temperature, warmed to room temperature, agitated for an additional 8h, filtered, dried in air, the residue

20 washed with water (3x3ml) and chromatographed twice (silica gel; first eluent: acetonitrile-water-acetic acid, 13:1:1; second eluent: chloroform-methanol-water, 100:20:1) to give the title compound (0.21g, 39%) as a solid material: m.p. 121-123°C. ¹H NMR (DMSO-D₆, TMS), δ: 2.80-3.43(12H, m); 3.07 (4H, t, J=5.8Hz); 6.83-7.85 (12H, m); 10.62 ppm (2H, br s). Anal. calculated for

25 C₂₆H₃₁N₅O₂*C₃H₆O₃: C 65.0; H 7.0; N 13.1. Found (%): C 65.0; H 6.6; N 13.4.

1:2 2-(1H-Indol-3-yl)-N-(2-[2-(2-1H-indol-3-yl-acetylamino) ethylamino]-ethyl)-acetamide 2.5 acetate, m.p. 105-107°C (on Fisher's table)

30 1:3 2-(1H-Indol-3-yl)-N-(3-[2-(2-1H-indol-3-yl-acetylamino) ethylamino]-propyl)-acetamide 2.5 acetate, m.p. 75-80°C (on Fisher's table)

1:4 N-(2-{Bis-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-amino}-ethyl)-2-(1H-

21

indol-3-yl)-acetamide hydrochloride, m.p. 121-123°C (on Fisher's table)

- 1:5 N-(2-{Bis-[2-(3-1H-indol-3-yl-propionylamino)-ethyl]-amino}-ethyl)-3-(1H-indol-3-yl)-propionamide 1.5 hydrochloride 1.5 hydrate, m.p. 113-116°C (on Fisher's table)
- 5
- 1:6 3-Guanidino-N-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-N-[3-(2-1H-indol-3-yl)-acetylamino]-propyl]-propionamide hydrochloride dihydrate, m.p. 145-151°C (on Fisher's table)
- 10
- 1:7 N-{7-Amino-3-[3-(2-1H-indol-3-yl-acetylamino)-propyl]-4-oxo-heptyl}-2-(1H-indol-3-yl)-acetamide hydrochloride hydrate, m.p. 125-130°C (on Fisher's table)
- 15
- 1:8 4-Amino-N,N-bis-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-butyramide 3.5 hydrochloride hydrate, m.p. 160-170°C (on Fisher's table)
- 20
- 1:9 N-(2-{[2-(2-Guanidino-acetylamino)-acetyl]-[3-(2-1H-indol-3-yl)-acetylamino]-propyl]-amino-ethyl tetrahydrochlorid hydrate 0.5 ethanol, m.p. 165-170°C (on Fisher's table)
- 25
- 1:10 2-(1H-Indol-3-yl)-N-{3-[3-(2-1H-indol-3-yl-acetylamino)-propylamino]-propyl}-acetamide hydrochloride hydrate, m.p. 191-192°C (on Fisher's table)
- 30
- 1:11 2-(1H-Indol-3-yl)-N-{6-[6-(2-1H-indol-3-yl-acetylamino)-hexylamino]-hexyl}-acetamide hydrochloride hydrate, m.p. 155-156°C (on Fisher's table)
- 1:12 3-Benzo[1,3]dioxol-5-yl-N-{2-[2-(3-benzo[1,3]dioxol-5-yl-acryloylamino)-ethylamino]-ethyl}-acrylamide hydrochloride hydrate, m.p. > 230°C
- 1:13 2-(1H-Indol-3-yl)-N-{4-[3-(2-1H-indol-3-yl-acetylamino)-propylamino]-

butyl}-acetamide hydrochloride hydrate, m.p. 208-209°C

1:14 2-Naphthalen-1-yl-N-{2-[2-(2-naphthalen-1-yl-acetylamino)-ethylamino]-ethyl}-acetamide hydrochloride hydrate, m.p. 180-181°C

5

1:15 2-(1H-Indol-3-yl)-N-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-acetamide, m.p. 213-214°C

1:16 N-[2-(2-1H-Indol-3-yl-acetylamino)-ethyl]-nicotinamide, m.p. 125-128°C

10

1:17 1H-Indole-3-carboxylic acid (2-{2-[(1H-indole-1-carbonyl)-amino]-ethylamino}-ethyl)-amide hydrochloride, m.p. 265°C

15

1:18 6-Chloro-2-methyl-pyridine-3-carboxylic acid (2-{2-[(6-chloro-2-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide hydrochloride, m.p. foam

1:19 4-(1H-Indol-3-yl)-N-{2-[2-(3-1H-indol-3-yl-propionylamino)-ethylamino]-ethyl}-butyramide hydrochloride hemihydrate, m.p. 151-153°C

20

1:20 1H-Indole-3-carboxylic acid {2-[2-(4-1H-indol-3-yl-butyrylamino)-ethylamino]-ethyl}-amide hydrochloride, m.p. 112°C

25

1:21 2-(2-Methyl-1H-indol-3-yl)-N-(2-{2-[2-(2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-acetamide hydrochloride dihydrate, m.p. 188-190°C

1:22 1H-Indole-3-carboxylic acid [2-(2-1H-indol-3-yl-acetylamino)-ethyl]-amide, m.p. 236°C

30

1:23 1H-Pyrrole-2-carboxylic acid (2-{2-[(1H-pyrrole-2-carbonyl)-amino]-ethylamino}-ethyl)-amide hydrochloride hydrate, m.p. 122°C

- 1:24 3-Bromobenzoic acid {2-[2-(3-bromo-benzoylamino)-ethylamino]-ethyl}-
amide hydrochloride, m.p. foam
- 5 1:25 3-Pyridin-3-yl-N-{2-[2-(3-pyridin-3-yl-propionylamino)-ethylamino]-
ethyl}-propionamide trihydrochloride, m.p 151°C
- 1:26 Pyridin-3-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-
amino]-ethylamino}-ethyl)-amide hydrochloride hydrate, m.p. foam
- 10 1:27 Benzoic acid [2-(2-benzoylamino-ethylamino)-ethyl]-amide hydrochloride,
m.p. foam
- 1:28 2-Iodo-benzoic acid {2-[2-(2-iodo-benzoylamino)-ethylamino]-ethyl}-
15 amide hydrochloride, m.p. foam
- 1:29 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[(1-methyl-1H-indazole-3-
carbonyl)-amino]-ethylamino} dihydrochloride, m.p. foam
- 20 1:30 N-[2-(1H-Indol-3-yl)-ethyl]-N'-{2-[2-(1H-indol-3-yl)-ethylamino]-ethyl}-
ethane-1,2-diamine
- 1:31 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-
1H-indol-3-yl)-acetylaminol-ethylamino}-ethyl)-amide
- 25 1:32 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[(1H-indole-3-carbonyl)-
amino]-ethylamino}-ethyl)-amide
- 1:33 1-Methyl-1H-indazole-3-carboxylic acid {2-[2-(4-1H-indol-3-yl-
30 butyrylamino)-ethylamino]-ethyl}-amide
- 1:34 1-Methyl-1H-indole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-

indol-3-yl)-acetyl-amino}-ethyl-amino}-ethyl)-amide

- 1:35 2-(5-Methoxy-2-methyl-1H-indol-3-yl)-N-(2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetyl-amino]-ethyl-amino}-ethyl)-acetamide
- 5
- 1:36 1H-Indole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetyl-amino]-ethyl-amino}-ethyl)-amide
- 1:37 4-(1H-Indol-3-yl)-N-(2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetyl-amino]-ethyl-amino}-ethyl)-butyramide
- 10
- 1:38 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[(1H-indole-3-carbonyl)-amino]-ethyl-amino}-ethyl)-amide
- 15
- 1:39 1H-Indole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetyl-amino]-ethyl-amino}-ethyl)-amide
- 1:40 1-Methyl-1H-indazole-3-carboxylic acid {2-[2-(4-1H-indol-3-yl)-butyrylamino]-ethyl-amino}-ethyl)-amide
- 20
- 1:41 4-(1H-Indol-3-yl)-N-(2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetyl-amino]-ethyl-amino}-ethyl)-butyramide
- 1:42 Pyridine-3-carboxylic acid (2-{2-[(4-butyl-pyridine-2-carbonyl)-amino]-ethyl-amino}-ethyl)-amide
- 25
- 1:43 Pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethyl-amino}-ethyl)-amide
- 30
- 1:44 Pyridine-3-carboxylic acid (2-{2-[(4-butyl-pyridine-2-carbonyl)-amino]-ethyl-amino}-ethyl)-amide

- 1:45 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(4-butyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:46 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
5
- 1:47 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 10 1:48 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:49 2-Chloro-6-methyl-pyridine-3-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 15 1:50 2-Chloro-6-methyl-pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:51 Pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
20
- 1:52 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 25 1:53 2-Chloro-6-methyl-pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:54 3-Chloro-5-trifluoromethyl-pyridine-2-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
30
- 1:55 2-Ethoxy-pyridine-3-carboxylic acid (2-{2-[(2-ethoxy-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide

EXAMPLE 2

This example illustrates the potency of compounds of formula (I) and their therapeutically active acid addition salts for treatment of mental disorders.

5

Test 1. Affinity for the MC1-receptor

The binding assay was carried out essentially as described by Lunec et al., Melanoma Res. 1992; 2; 5-12 using I^{125} -NDP- α MSH as ligand.

10

Test 2. Affinity for the MC3-receptors, the MC4-receptors and the MC5-receptors

The binding assays were carried out essentially as described by Szardenings et al., J. Biol. Chem. 1997; 272; 27943-27948 and Schiöth et al., FEBS Lett. 1997; 410; 223-228 using I^{125} -NDP- α MSH as ligand.

Essentially, the affinity of the compounds to the different receptors were determined using either insect cells (Sf9) or COS cells, which were transfected with recombinant human MC3, MC4 or MC5 receptors. For the determination of the affinity to the MC1 receptor, B16 mouse melanoma cells were used, which endogenously express the (mouse) MC1 receptor.

The compounds were tested at different concentrations for their ability to displace I^{125} -labelled NDP-MSH from the respective receptor. Incubation was performed in 96-well plates using 50,000 cells/well (Sf9 or COS cells) up to 200,000 cells/well (mouse melanoma cells).

The test compound or standard (NDP-MSH) was added in an appropriate concentration (generally between 10^{-4} M and 10^{-12} M) together with labelled tracer (approx. 50,000 cpm/well) and incubation was performed for 2 hours (at room

30

temperature for Sf 9 cells and at +37°C for COS cells and mouse melanoma cells).

After the incubation, the cells were washed twice to get rid of excess tracer and
5 compound, and the cells were lysed with 0.1M NaOH. The lysate was counted in
a gamma-counter, binding was calculated and the affinity then determined.

Test 3. cAMP Assay

10

The stimulation of cAMP was carried out essentially as described by Schiöth et al., Br. J. Pharmacol. 1998; 124; 75-82.

Essentially, the effects of the compounds were tested in vivo for their ability to
15 stimulate the production of cAMP. The cells used were the same ones that were
used for the binding assays (see above), i.e. for the MC1 receptor, mouse
melanoma B16 cells were used and for the MC3, MC4 and MC5 receptors, Sf9
or COS cells, transfected with the respective human receptors.

20 Cyclic AMP was stimulated by the addition of the compounds at different
concentrations in the presence of a phosphodiesterase inhibitor, during a period of
20 minutes at +37°C. cAMP was extracted with PCA, neutralised with KOH
and the mixture was then centrifuged.

25 The concentration of cAMP was determined using a binding assay comprising
binding protein (from bovine adrenals). Tritiated cAMP, used as tracer, and
extracts (from above) in different dilutions were incubated at +4°C for 120-150
minutes. The cAMP in the unknown samples displaced the labelled cAMP from
binding to the binding protein. The binding protein-cAMP/tracer complex was
30 harvested using a filter technique and the filters were counted using a beta-
counter. The concentrations of cAMP in the unknown extracts were calculated
using a standard curve of known concentrations.

Table 1 Affinity for MC-receptors

	<u>Compound</u>	<u>Ki(μM)</u>			
		<u>MC1</u>	<u>MC3</u>	<u>MC4</u>	<u>MC5</u>
5	1:2	219	332	346	267
	1:12	3.0	81.3	92.6	87.1
	1:14	4.2	17.2	11.7	8.2
	1:24	0.5	2.0	3.5	2.2

10 Table 1b: Influence on cAMP (given as percent of base level)

	<u>Comp.</u>	<u>MC1c</u>	<u>MC3c</u>	<u>MC4c</u>	<u>MC5c</u>
	1:2	134	215	209	164
	1:12	173	185	117	223
15	1:15	141	178	227	135
	1:1	416	16		376

EXAMPLE 3

20

In vivo effects on food intake

Compounds have been tested for their effects on food intake and body weight in rats. In order to investigate the *agonistic* effect, ie decrease in food intake, of
 25 compounds, the nocturnal protocol was used.

Sprague-Dawley, male rats were used, which were cannulated
 intracerebroventricularly. Stainless steel guide cannulae were placed in the lateral
 ventricle and fixed in the skull. Animals were acclimatized for a week before the
 30 experiments took place. After the experiments were done, the rats were killed and
 placement of the cannulae were checked.

Nocturnal protocol:

Rats were cannulated as described above. They were used without prior starvation, and compounds were administered at 5 pm in a total volume of 5µl. Doses of Compound 1:2 used were 0.25, 1 and 4 nmoles. For Compound 1:15, 10 and 50 nmoles were used. Food intake was measured at 3, 15 and 24 hours after dosing, and body weight was recorded at 24 hours. For comparison, the well known MC4 receptor agonist, Melanotan II (MTII) was used, at a dose of 1 nmole.

10 Results:

Intracerebroventricular administration of Compound 1:2 resulted in significantly reduced (cumulative) food intake at 15 and 24 hours. Only the lowest dose showed a significant effect also at the earliest time point (3 hours). Body weight gain decreased accordingly.

The decrease in food intake and body weight gain after the administration of Compound 1:2 was in the same range as that seen for MTII, as demonstrated in Figures 1 to 4.

20

The long term effects after a single administration of Compound 1:2 is shown in Fig 5. It is clearly seen that there is a dose dependent normalisation of food intake, i.e. food intake is normalized after two days with a low dose (1 nmole), but not until after 3 days with the higher dose (4 nmoles).

25

The effect of single injections of Compound 1:15 did not exhibit significant effects neither on cumulative food intake, nor on body weight gain. The results are shown in Figures 6 and 7.

30 In order to evaluate the selectivity of the compounds in vivo, an antagonist (HS014) was given prior to administration of Compound 1:2 and food intake was

30

recorded during the next 4 hours. Administration was done icv, in the morning after normal eating during the night.

5 The antagonist (HS014, 1 nmole) was given (icv) 10-30 minutes prior to the agonist (Compound 1:2, 4 nmoles). The results showed that HS014 slightly increased food intake whereas Compound 1:2 decreased food intake. When given simultaneously, the decrease in food intake of Compound 1:2 was blocked and the cumulative food intake was approximately the same as in vehicle treated rats (Figure 8).

10

The following formulations are representative of all of the pharmacologically active compounds of the invention.

Example 4

15

Example of a preparation comprising a capsule

	<u>Per capsule</u>
Active ingredient, as salt	5 mg
20 Lactose	250 mg
Starch	120 mg
Magnesium stearate	5 mg
<hr/>	
Total	up to 385 mg

25

In cases where higher amounts of active ingredient are required, the amount of lactose used may be reduced.

30

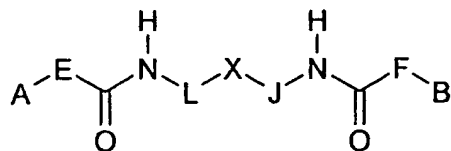
Example of a suitable tablet formulation.

	<u>Per tablet</u>
5 Active ingredient, as salt	5 mg
Potato starch	90 mg
Colloidal Silica	10 mg
Talc	20 mg
Magnesium stearate	2 mg
10 5 % aqueous solution of gelatine	25 mg
<hr/>	
Total up to	385 mg

- 15 A solution for parenteral administration by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable acid addition salt of the active substance preferably in a concentration of 0.1 % to about 5 % by weight. These solutions may also contain stabilising agents and/or buffering agents.

Claims:

1. A compound of general formula (I)

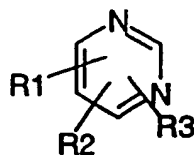
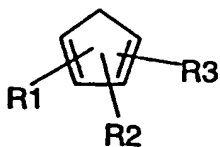
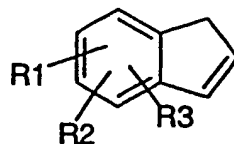
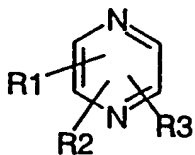
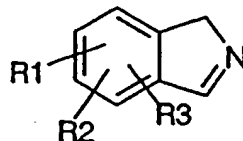
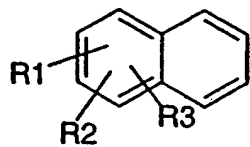
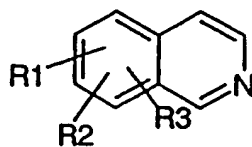
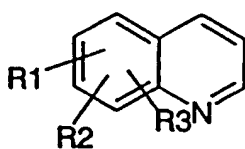


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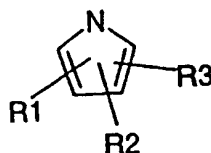
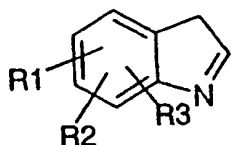
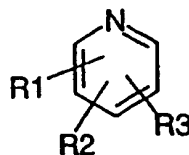
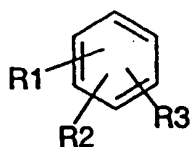
wherein E, L, J and F are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4 or 5 carbon atoms;

A and B are the same or different and are independently selected from the following:

10



5



10

wherein R_1 , R_2 and R_3 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 5 carbon atoms, electron donor groups such as alkoxy having 1-5 carbon atoms or hydroxy, electron acceptor groups selected from cyano, nitro, trifluoroalkyl or amide;

15

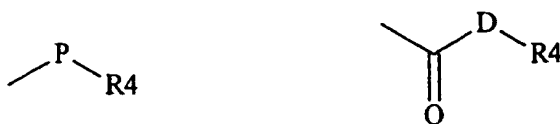
X is selected from methylene, amino, carbonyl, nitrogen, oxygen, or from the following:

20



R is selected from the following:

25

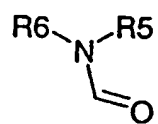
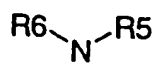


wherein P and D are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4 or 5 carbon atoms, or D may be absent (i.e. D is a single bond);

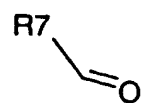
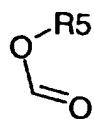
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R_4 is hydroxy, methyl, cyclohexyl, cyclopentyl, aminoguanidine, carboxylic or R_4 is selected from:

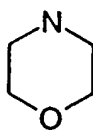
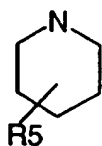
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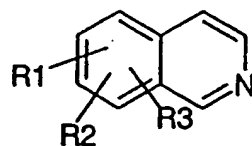
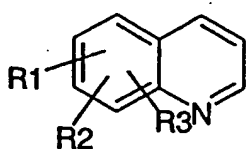
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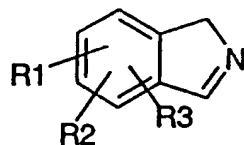
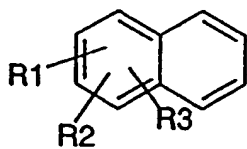
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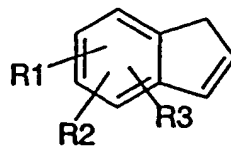
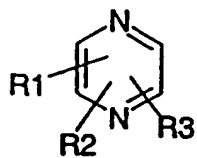
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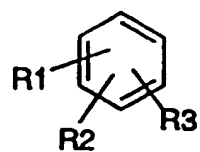
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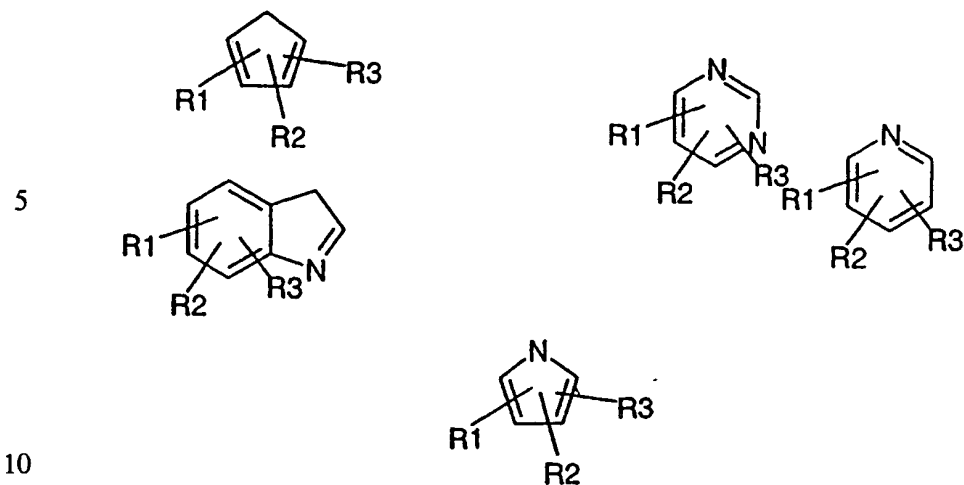


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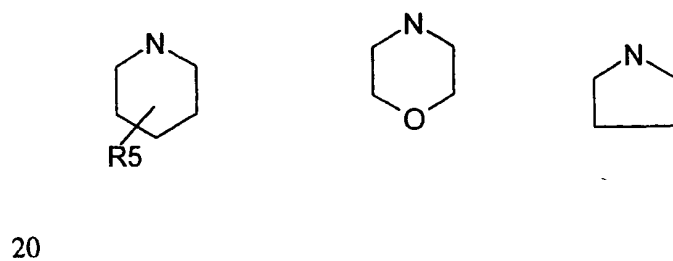
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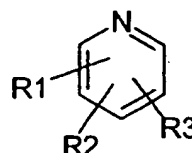
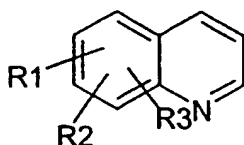
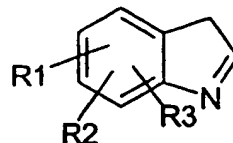
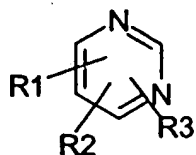
R5 and R6 are the same or different and are selected from hydrogen, lower alkyl such as methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl, iso-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and hexyl; and R1, R2 and R3 are
 15 as defined above;

R7 is selected from:



or a pharmacologically active salt thereof.

2. A compound as claimed in claim 1, wherein A and B are the same or
 25 different and are selected from:



3. A compound as claimed in any one of the previous claims, wherein one or more of R1, R2 and R3 are alkyl having 1 to 5 carbon atoms.

4. A compound as claimed in claim 3, wherein the alkyl is methyl or ethyl.

5. A compound as claimed in any one of the previous claims wherein one or more of R1, R2 and R3 are alkoxy.

6. A compound as claimed in claim 5, wherein the alkoxy is methoxy.

7. A compound as claimed in any one of the previous claims wherein one or more of R1, R2 and R3 are halogen atoms.

8. A compound as claimed in claim 7 wherein the halogen is fluoro or chloro.

9. A compound having one of the following formulae:

1:1 3-(1H-Indol-3-yl)-N-{2-[2-(3-1H-indol-3-yl-propionylamino)-ethylamino]-ethyl}-propionamide

1:2 2-(1H-Indol-3-yl)-N-(2-[2-(2-1H-indol-3-yl-acetylamino) ethylamino]-ethyl)-acetamide

- 1:3 2-(1H-Indol-3-yl)-N-(3-[2-(2-1H-indol-3-yl-acetylamino) ethylamino]-propyl)-acetamide
- 1:4 N-(2-{Bis-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-amino}-ethyl)-2-(1H-indol-3-yl)-acetamide
- 5
- 1:5 N-(2-{Bis-[2-(3-1H-indol-3-yl-propionylamino)-ethyl]-amino}-ethyl)-3-(1H-indol-3-yl)-propionamide
- 10 1:6 3-Guanidino-N-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-N-[3-(2-1H-indol-3-yl-acetylamino)-propyl]-propionamide
- 1:7 N-{7-Amino-3-[3-(2-1H-indol-3-yl-acetylamino)-propyl]-4-oxo-heptyl}-2-(1H-indol-3-yl)-acetamide
- 15
- 1:8 4-Amino-N,N-bis-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-butyramide
- 1:9 N-(2-{[2-(2-Guanidino-acetylamino)-acetyl]-[3-(2-1H-indol-3-yl-acetylamino)-propyl]-amino-ethyl
- 20
- 1:10 2-(1H-Indol-3-yl)-N-{3-[3-(2-1H-indol-3-yl-acetylamino)-propylamino]-propyl}-acetamide
- 1:11 2-(1H-Indol-3-yl)-N-{6-[6-(2-1H-indol-3-yl-acetylamino)-hexylamino]-hexyl}-acetamide
- 25
- 1:12 3-Benzo[1,3]dioxol-5-yl-N-{2-[2-(3-benzo[1,3]dioxol-5-yl-acryloylamino)-ethylamino]-ethyl}-acrylamide
- 30 1:13 2-(1H-Indol-3-yl)-N-{4-[3-(2-1H-indol-3-yl-acetylamino)-propylamino]-butyl}-acetamide
- 1:14 2-Naphthalen-1-yl-N-{2-[2-(2-naphthalen-1-yl-acetylamino)-ethylamino]-

ethyl}-acetamide

- 1:15 2-(1H-Indol-3-yl)-N-[2-(2-1H-indol-3-yl-acetylamino)-ethyl]-acetamide
- 5 1:16 N-[2-(2-1H-Indol-3-yl-acetylamino)-ethyl]-nicotinamide
- 1:17 1H-Indole-3-carboxylic_acid_(2-{2-[(1H-indole-1-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 10 1:18 6-Chloro-2-methyl-pyridine-3-carboxylic acid (2-{2-[(6-chloro-2-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:19 4-(1H-Indol-3-yl)-N-{2-[2-(3-1H-indol-3-yl-propionylamino)-ethylamino]-ethyl}-butyramide
- 15 1:20 1H-Indole-3-carboxylic_acid_{2-[2-(4-1H-indol-3-yl-butyrylamino)-ethylamino]-ethyl}-amide
- 1:21 2-(2-Methyl-1H-indol-3-yl)-N-(2-{2-[2-(2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-acetamide
- 20 1:22 1H-Indole-3-carboxylic acid [2-(2-1H-indol-3-yl-acetylamino)-ethyl]-amide
- 25 1:23 1H-Pyrrole-2-carboxylic acid (2-{2-[(1H-pyrrole-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:24 3-Bromobenzoic acid {2-[2-(3-bromo-benzoylamino)-ethylamino]-ethyl}-amide
- 30 1:25 3-Pyridin-3-yl-N-{2-[2-(3-pyridin-3-yl-propionylamino)-ethylamino]-ethyl}-propionamide

- 1:26 Pyridin-3-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 5 1:27 Benzoic acid [2-(2-benzoylamino-ethylamino)-ethyl]-amide
- 1:28 2-Iodo-benzoic acid {2-[2-(2-iodo-benzoylamino)-ethylamino]-ethyl}-amide
- 10 1:29 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[(1-methyl-1H-indazole-3-carbonyl)-amino]-ethylamino}
- 1:30 N-[2-(1H-Indol-3-yl)-ethyl]-N'-{2-[2-(1H-indol-3-yl)-ethylamino]-ethyl}-ethane-1,2-diamine
- 15 1:31 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-amide
- 1:32 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[(1H-indole-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 20 1:33 1-Methyl-1H-indazole-3-carboxylic acid {2-[2-(4-1H-indol-3-yl-butylamino)-ethylamino]-ethyl}-amide
- 25 1:34 1-Methyl-1H-indole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-amide
- 1:35 2-(5-Methoxy-2-methyl-1H-indol-3-yl)-N-(2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-acetamide
- 30 1:36 1H-Indole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-amide

- 1:37 4-(1H-Indol-3-yl)-N-(2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-butyramide
- 5 1:38 1-Methyl-1H-indazole-3-carboxylic acid (2-{2-[(1H-indole-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:39 1H-Indole-3-carboxylic acid (2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-amide
- 10 1:40 1-Methyl-1H-indazole-3-carboxylic acid {2-[2-(4-1H-indol-3-yl-butyrylamino)-ethylamino]-ethyl}-amide
- 15 1:41 4-(1H-Indol-3-yl)-N-(2-{2-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-acetylamino]-ethylamino}-ethyl)-butyramide
- 1:42 Pyridine-3-carboxylic acid (2-{2-[(4-butyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 20 1:43 Pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:44 Pyridine-3-carboxylic acid (2-{2-[(4-butyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 25 1:45 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(4-butyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:46 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 30 1:47 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-

pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide

- 1:48 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 5
- 1:49 2-Chloro-6-methyl-pyridine-3-carboxylic acid (2-{2-[(2-chloro-6-methyl-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:50 2-Chloro-6-methyl-pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 10
- 1:51 Pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 15 1:52 4-Butyl-pyridine-2-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:53 2-Chloro-6-methyl-pyridine-3-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 20
- 1:54 3-Chloro-5-trifluoromethyl-pyridine-2-carboxylic acid (2-{2-[(3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 1:55 2-Ethoxy-pyridine-3-carboxylic acid (2-{2-[(2-ethoxy-pyridine-3-carbonyl)-amino]-ethylamino}-ethyl)-amide
- 25

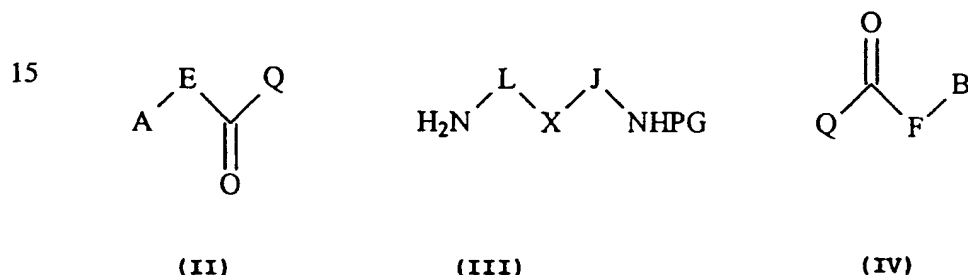
or a pharmaceutically acceptable salt thereof.

10. A compound as claimed in any one of the previous claims which
- 30 additionally comprises a label, preferably a radioactive label, or a toxic agent.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10, together with one or more adjuvants, carriers or excipients.

12. A compound as claimed in any one of claims 1 to 10 for use as a
5 medicament.

13. A process for the production of a compound as claimed in any one of claims 1 to 10 wherein a compound of formula (II), wherein A and E are as defined in claim 1 and Q is a leaving group, is reacted with a compound of formula (III),
10 wherein L, J and X are as defined in claim 1 and PG is a protecting group; the protecting group is then removed by standard procedures and followed by reacting with compound (IV), wherein F and B are as defined in claim 1 and Q is a suitable leaving group.



20

14. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of inflammation.

15. Use of a compound as claimed in any one of claims 1 to 10 in the
25 production of a medicament for the treatment of mental disorders.

16. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of dysfunctions of the endocrine system or an hormonal system.

30

17. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of sexual functions and/or sexual dysfunctions.
- 5 18. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of drug-induced or other disorders of the blood and/or lymphoid system.
- 10 19. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of allergic disorders.
20. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of disorders of the cardiovascular system.
- 15 21. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of pain.
- 20 22. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for inducing skin tanning or for inducing lighter skin colour.
23. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of diabetes type II.
- 25 24. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of obesity.
- 30 25. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of anorexic conditions such as those caused by cancer, cachexia, geriatric conditions, HIV, trauma and psychological conditions.

26. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for inducing peripheral nerve regeneration.
- 5 27. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for inducing central nerve regeneration.
28. A method of treating inflammation comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 10 29. A method of treating mental disorders comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
30. A method of treating dysfunctions of the endocrine system or an hormonal system comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 15 31. A method of treating sexual functions and/or sexual dysfunctions comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 20 32. A method of treating drug-induced or other disorders of the blood and/or lymphoid system comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 25 33. A method of treating disorders of the cardiovascular system comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
34. A method of treating pain comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 30

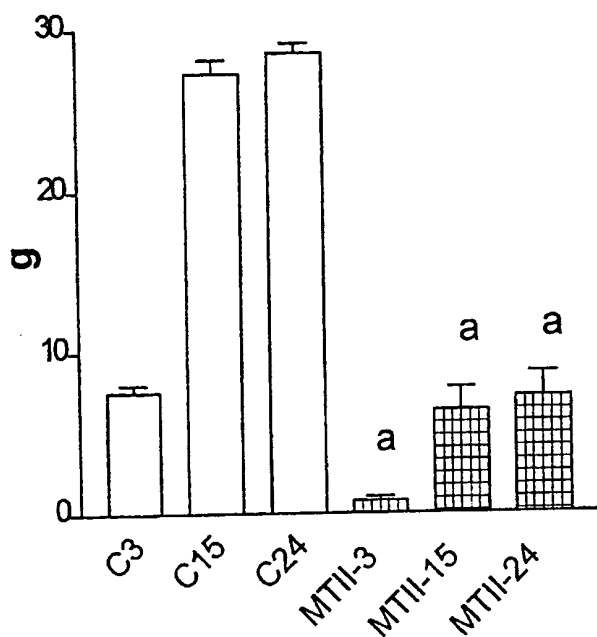
35. A method of inducing skin tanning or for inducing lighter skin colour comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 5 36. A method of treating diabetes type II comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
37. A method of treating obesity comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 10 38. A method of treating anorexic conditions such as those caused by cancer, cachexia, geriatric conditions, HIV, trauma and psychological conditions comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 15 39. A method of inducing peripheral nerve regeneration comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
40. A method of inducing central nerve regeneration comprising the use or
20 administration of a compound as claimed in any one of claims 1 to 10.
41. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of skin disorders, including for the treatment of melanoma.
- 25 42. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment and/or diagnosis of malignancies, such as melanoma and metastases.
- 30 43. A method of treating a skin disorder, including the treatment of melanoma, comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

44. A method of treating and/or diagnosing malignancies, such as melanoma and metastases, comprising the use or administration of a compound as claimed in any one of claims 1 to 10.
- 5
45. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of ischemia and/or ischemia/reperfusion.
- 10 46. A method of treating ischemia and/or ischemia/reperfusion comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

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Food intake after icv administration

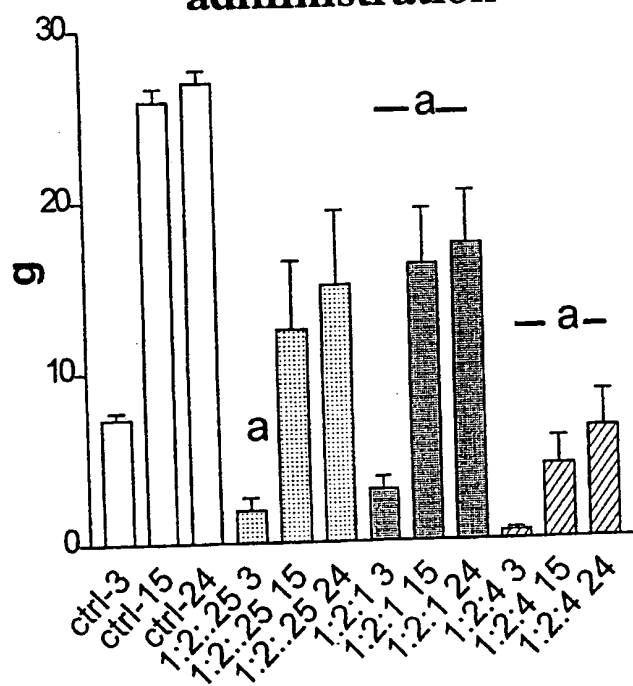
Figure 1



a: $p < 0.001$ vs control

Food intake after icv administration

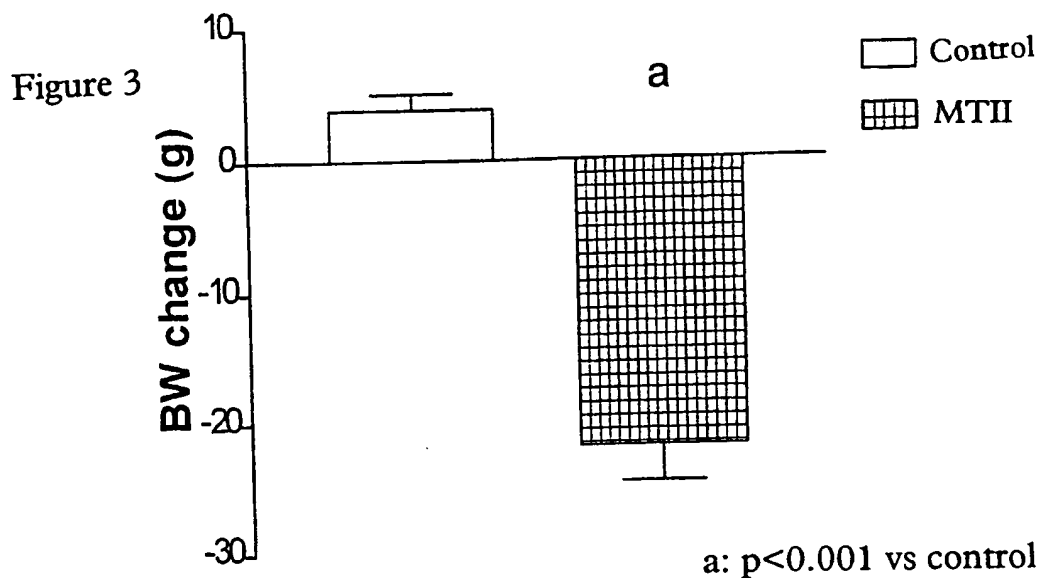
Figure 2



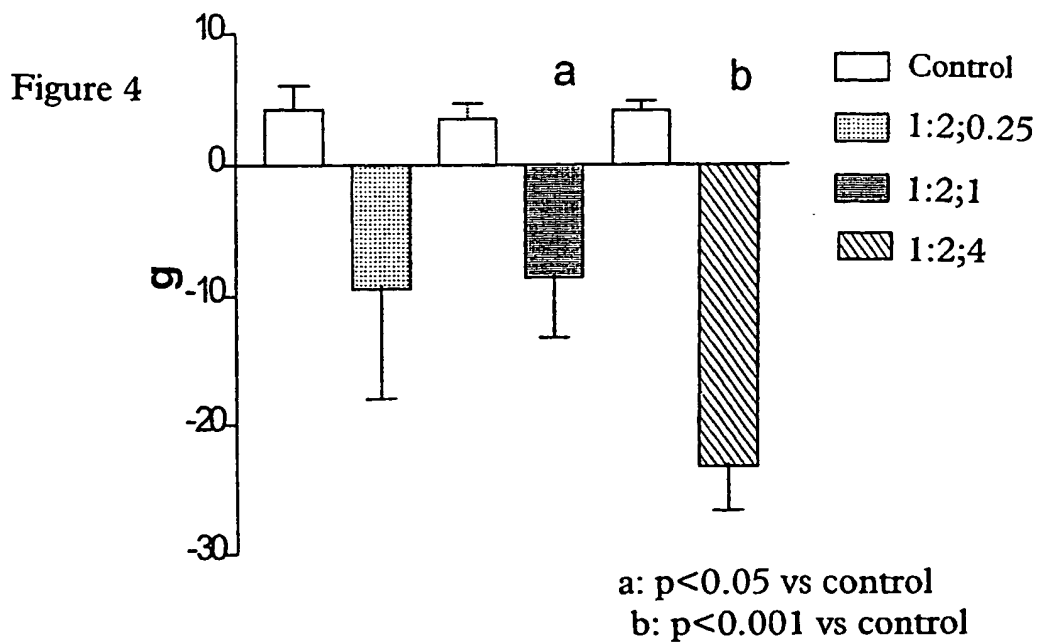
a: $p < 0.05$ vs control

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Effect on body weight after icv administration

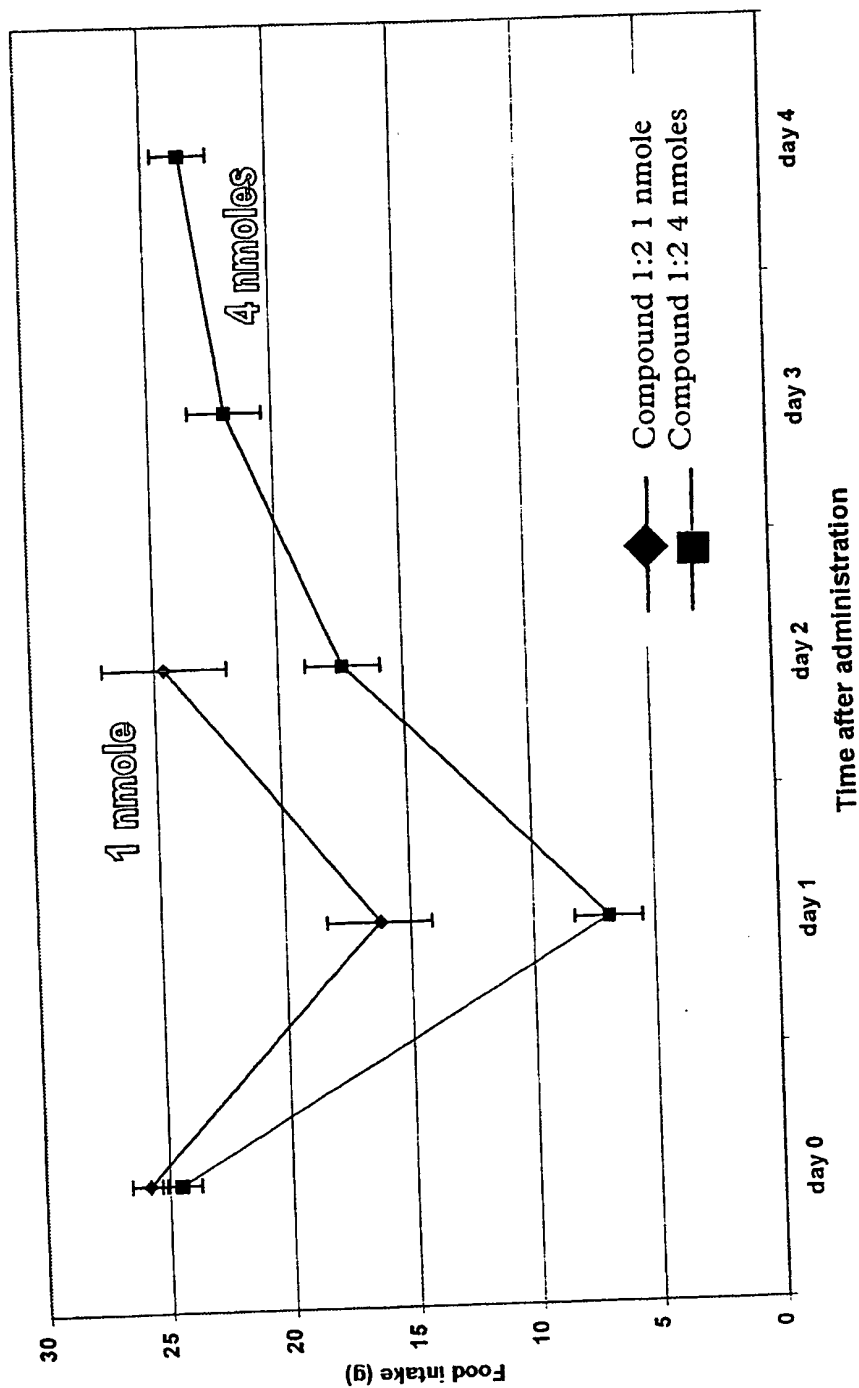


Body weight change compound 1:2



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Figure 5



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Figure 6

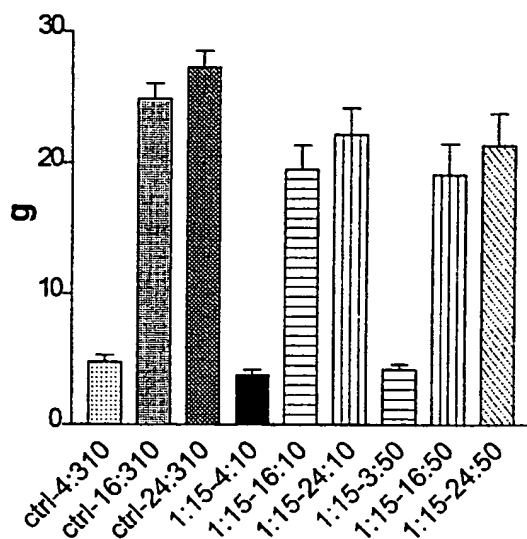
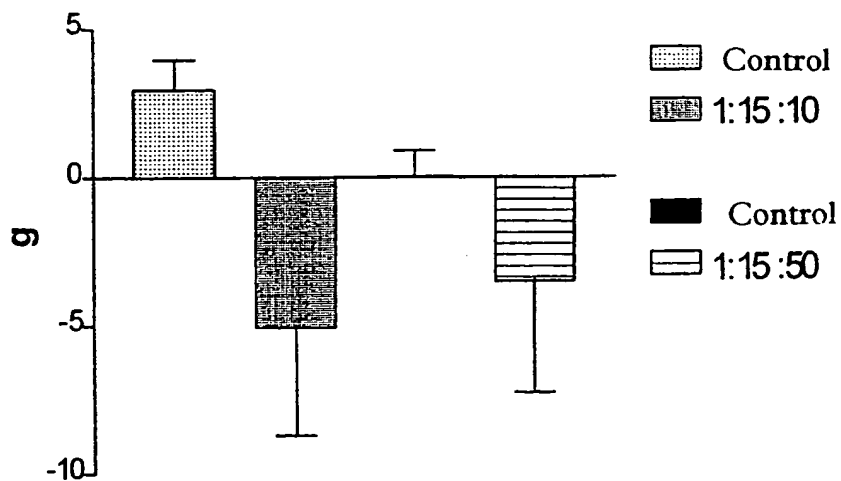
1:15 : Cumulative food intake

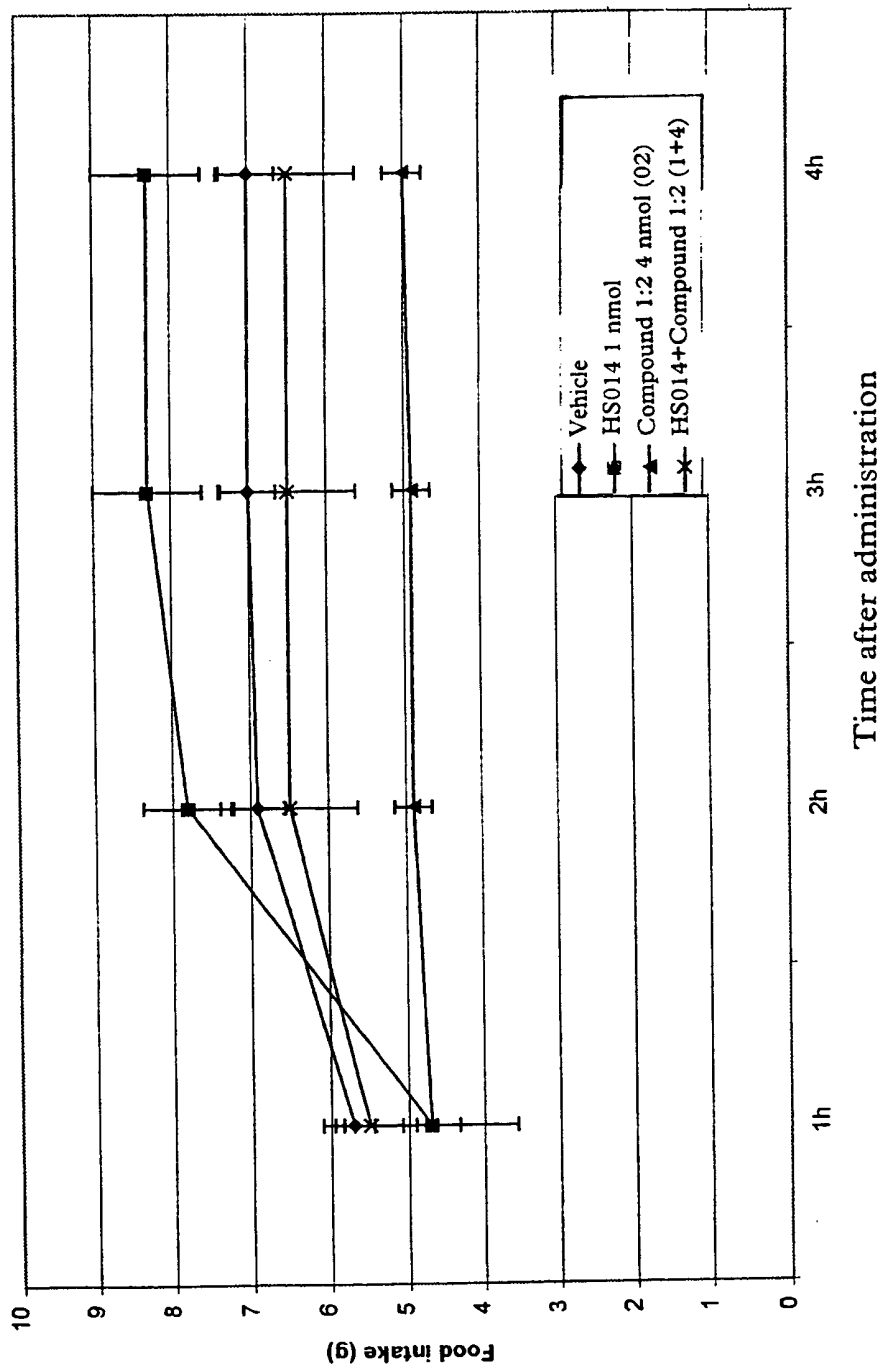
Figure 7

Body weight change

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Figure 8

Combined effects of HS014 and Compound 1:2 (1+4 nmoles)



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/00350

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/18 A61K31/405 A61P3/04 C07D209/40 C07D317/60
A61K31/36 C07C233/40 C07D401/12 C07D213/61 A61K31/44
C07D207/34 A61K31/34 C07D231/56 A61K31/415 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 64002 A (PATCHETT ARTHUR A ; PLOEG LEONARDUS H T V D (US); YE ZHIXIONG (US);) 16 December 1999 (1999-12-16) cited in the application claim 1	9
A	WO 99 55679 A (TREGA BIOSCIENCES INC) 4 November 1999 (1999-11-04) cited in the application claim 1	9
A	EP 0 820 767 A (OREAL) 28 January 1998 (1998-01-28) page 2, line 21; claim 1	9
	--- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

11 April 2001

Date of mailing of the international search report

23 April 2001 (23.04.01)

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/00350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	<p>WO 00 74679 A (PATCHETT ARTHUR A ; PLOEG LEONARDUS H T V D (US); SEBHAT IYASSU (US) 14 December 2000 (2000-12-14) claim 1</p> <p>-----</p>	9

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 01/00350

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28-40, 43, 44 and 46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-8
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-8

Present claims 1-9 relate to an extremely large number of possible compounds and their uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. It is additionally noted that claims 1-2 relate to a compounds defined by reference to a desirable characteristic or property, namely "electron donor group". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. The only claim which can be considered to be adequately supported by the description is the independent claim 9. It is additionally noted that some of the compounds of claim 9 do not fall within the scope of formula (I) in claim 1. It is therefore not clear whether or not the compounds (I) represent the full scope of what is claimed. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the specific examples outlined in claim 9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/00350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9964002 A	16-12-1999	AU 4680199 A EP 1085869 A	30-12-1999 28-03-2001
WO 9955679 A	04-11-1999	AU 3768799 A EP 1076649 A US 6127381 A	16-11-1999 21-02-2001 03-10-2000
EP 0820767 A	28-01-1998	FR 2751535 A CA 2210848 A JP 2963677 B JP 10067649 A US 5932608 A	30-01-1998 25-01-1998 18-10-1999 10-03-1998 03-08-1999
WO 0074679 A	14-12-2000	NONE	

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